Bidirectional communication: Growth and immunity in domestic livestock

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Bidirectional communication: Growth and immunity in domestic livestock[1,2,3,4]

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ABSTRACT: Evidence continues to mount supporting the existence of a bidirectional communication network between the immune system and the somatotropic axis in a variety of species. For more than 4 decades, researchers have sought and identified linkages between the growth axis and the immune system. Although significant advances have been made with regard to elucidation of various bidirectional communication pathways between the immune system and growth axis in humans and rodents, the current paper focuses on the relationships between the immune system and somatotropic axis in sheep, cattle, and swine. Aspects from historical and current research associated with changes in somatotropic function following immune challenges with endotoxin, parasites, viruses, and bacteria have been provided. Collectively, these studies demonstrate that a bidirectional communication network, similar to that described in humans and rodents, also exists in a variety of domestic livestock. Identifying and understanding this bidirectional communication network could have significant economic benefits if it leads to intervention strategies to prevent production losses associated with sickness and disease.

Key words: cytokine, cattle, growth, immune function, pig, sheep

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INTRODUCTION

The intent of this brief review is to highlight only those established relationships that have been reported between the immune system, primarily the acute phase immune response, and the somatotropic axis in sheep, cattle, and pigs. Hormonal regulation of the immune system and the relationship between immunity and productivity in avian species have been exceptionally well covered by others (Klasing, 1998) and, therefore, will not be addressed in the current review. For a review of the literature pertaining to proinflammatory cytokine alterations of the somatotropic axis in humans and rodents, the reader is referred to Frost and Lang (2004). Additionally, a more in-depth examination of and historical perspective associated with the relationship between protein hormones and the immune system have recently been provided by Kelley et al. (2007).

HISTORICAL PERSPECTIVE

The existence of communication pathways among various hormonal products of the endocrine system and the immune system have been documented in a variety of species for more than 4 decades. As early as 1965, investigators revealed a connection between endocrine hormones and the functionality of the immune system (Nicol et al., 1965). In the 1970s, researchers were already exploring the mechanistic pathways by which protein hormones could modulate immunity and had specifically linked GH to cellular immunity, immunological memory, and activation of lymphocytes (Astaldi et al., 1972; Shemerovskaia and Kovaleva, 1975).

Investigation into possible communication pathways between the endocrine and immune systems during the 1980s and 1990s tended to focus primarily on the various effects of exogenous GH and IGF-I on in vitro and in vivo aspects of immunity. Evidence was also increasing with regard to the immunomodulatory roles of prolactin (**PRL**) and thyroid-stimulating hormone (**TSH**; Kelley et al., 2007). Evidence of an uncoupling of the GH/IGF-I axis during an immunological insult, resulting in elevated concentrations of GH in the presence of low circu-

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[2]Mention of trade names or proprietary products does not constitute a guarantee or warranty of the product by the USDA and does not imply its approval to the exclusion of other products that also may be suitable.

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Table 1. Effect of an immunological insult on circulating concentrations of anterior pituitary gland hormones and tumor necrosis factor-alpha (TNF) in various species

Human, sheep, pig	Rat, cattle, bird
Increased ACTH	Increased ACTH
Decreased LH	Decreased LH
Increased prolactin	Increased prolactin
Increased TNF	Increased TNF
Increased GH	Decreased GH

lating concentrations of IGF-I, was also mounting. However, it should be noted that changes in circulating concentrations of GH have been reported to be species specific (Daniel et al., 2002). For example, in humans, sheep, and pigs, GH concentrations have been reported to increase following activation of the immune system, whereas in rats, cattle, and birds, GH concentrations have been reported to decrease (Table 1).

During this period, research expanded beyond the link between GH and the immune system to include potential specific linkages between IGF-I and the immune system as well. Edwards and coworkers (1988) demonstrated that IGF-I could directly stimulate macrophages and neutrophils isolated from rats, thus indicating the existence of IGF type receptors on immune cells. Indeed, subsequent research reported the isolation of type I IGF receptors on monocytes and B-lymphocytes (Stuart et al., 1991). Further investigation revealed that IGF-I may also play a role in the regulation of T cell development at the level of the thymus (Kooijman et al., 1995). By 1999, it was reported that virtually all immune cells express the IGF-I receptor and could be regulated by IGF-I (Heemskerk et al., 1999). More recently, investigators have expanded the knowledge base in this area by demonstrating that a large portion of T lymphocytes express the type I IGF receptor, which indicates a possible role for these receptors in the proliferation of memory T cells (Douglas et al., 2007).

While the initial research focus was directed primarily at the effects of protein hormones, such as GH, IGF-I, PRL, and TSH on modulating various aspects of immunity, it has become exceedingly evident that communication between the endocrine and immune systems represents a bidirectional communication pathway that supports not only health, but optimal growth as well. Evidence of this bidirectional communication pathway has accumulated at a rapid pace in recent years with the use of various immune challenge models, animal disease models, gene knockout models, and the availability of new technologies. For example, recent studies have demonstrated that the proinflammatory cytokines IL-1β and IL-6 can impair IGF-I stimulated muscle growth, and may alter IGFBP profiles, thereby indirectly altering the bioactivity of IGF-I (Broussard et al., 2004). Additionally, in contrast to the catabolic actions of IL-1β and IL-6 on muscle tissue, IL-15, a cytokine produced in various tissues including placenta, skeletal muscle, kidney, lung, heart, and macrophages has been reported to act in an additive fashion with IGF-I on muscle fiber growth (Quinn et al., 1995). As these additional pathways are elucidated, it becomes evident that communication between the immune and endocrine system is a complex, multifaceted system that involves a plethora of hormones and cytokines influenced by numerous inputs including genetics, nutritional status, stress, developmental stage, and the overall health status of the animal.

OVERVIEW OF THE ACUTE PHASE RESPONSE

Given the primary focus of this overview on the relationship between the acute phase immune response and the somatotropic axis, a brief review of the innate immune system and events associated with the acute phase immune response was deemed appropriate. Innate immunity is considered to be the first line of defense against pathogens, whether bacterial, viral, protozoal, or fungal. It includes physical barriers such as the skin, mucosal secretions, tears, urine, and stomach acid, as well as complement and antigen-nonspecific cellular components and is designed to elicit an immediate or acute response (0 to 4 h) following exposure to an antigenic agent. Until recently, the innate immune system was thought to represent the antigen-nonspecific aspect of the immune system. However, recent evidence suggests that the innate response may be specific to the pathogenic agent encountered. Although it is often assumed that this aspect of the immune system becomes a constant entity once developed by the animal, this is certainly not the case. The innate immune system, although always present to some degree, can be modulated in a beneficial or detrimental manner by a number of factors including wounds, dehydration, nutritional status, genetics, stress, and various peptide hormones.

The cellular component of the innate immune system consists of phagocytic cells (e.g., neutrophils, monocytes, macrophages, and dendritic cells), natural killer cells, and cells that release inflammatory mediators (i.e., basophils, mast cells, and eosinophils). Unlike adaptive immunity, phagocytic cells of the innate immune system do not recognize every possible antigen. Instead, they recognize a few highly conserved structures called pathogen-associated molecular patterns (**PAMP**; Janeway et al., 2005) that are present in many different microorganisms and interact with receptors on the surface of the immune cells. Some common examples of PAMP molecules that are recognized by innate immune cells include lipopolysaccharide (**LPS**) from the gram-negative cell wall, peptidoglycan, lipotechoic acids from the gram-positive cell wall, the sugar mannose, bacterial DNA, double-stranded RNA from viruses, and glucans from fungal cell walls. Most body defense cells express receptors for these common PAMP, thus invoking an immediate response against

the invading microorganism. The ability of the innate immune system to recognize LPS has led to its extensive use in numerous animal research models to elucidate communication pathways associated with the acute phase immune response. The release of proinflammatory cytokines, IL-1β, IL-6, IL-12, tumor necrosis factor-α (**TNF-α**), and interferon-γ by cells of the innate immune system initiates the acute phase response (**APR**) and the adaptive immune response (Baumann and Gauldie, 1994; Elenkov and Chrousos, 1999; Suffredini et al., 1999). The initial release of proinflammatory cytokines is augmented by their paracrine actions on neighboring immune cells, causing further release of these cytokines and ultimately resulting in the systemic release of cytokines.

Initiation of the APR by the release of proinflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α) from macrophages and monocytes at the site of inflammation or infection is characterized by varied reactions of the body. These reactions most notably include fever, increased liver synthesis of the acute phase proteins, increases in circulating white blood cells, and changes in behavior such as increased sleep, decreased food and water intake, decreased social and sexual behavior, decreased aggressive behavior, and increased pain reactivity. Additionally, the APR is typically coupled with an increase in the release of pituitary-adrenal and sympathetic hormones, a result of increased activity of the stress axis. The febrile response and alterations in liver metabolism and gene regulation are the 2 primary physiological responses associated with acute inflammation. The febrile response involves alteration of the temperature set point in the hypothalamus, and is mediated by the proinflammatory cytokines, IL-6 and TNF-α, through the induction of prostaglandin E_2. Elevating the body temperature through the generation of fever aids in reducing the survival and reproduction of most microbial organisms and attempts to prevent or reduce the febrile response with antipyretic drugs has been reported to be detrimental (Kluger and Rothenburg, 1979). For example, administering antipyretic drugs to goats infected with *Trypansosoma vivax* increased the mortality from infection (van Miert et al., 1978). This phenomenon may not only be associated with the ability to destroy bacteria and microorganisms within the host, but may reflect a reduction in fever-induced acceleration of the cellular proliferation of immune cells within the host. In addition to fever induction, IL-6 can also act on the pituitary to increase ACTH secretion and, subsequently, cortisol from the adrenal cortex. An increase in circulating cortisol, although often overlooked, is an important component of the APR because glucocorticoids provide a negative feedback loop to inhibit further cytokine gene expression.

The second physiological response coupled to the APR is characterized by alterations in liver metabolism and gene regulation. During an inflammatory response, IL-6 and TNF-α mediate hepatocyte production and secretion of acute phase proteins. Production of the acute phase proteins can increase or decrease in response to inflammation, bacterial infection, endotoxin exposure, neoplasia, or physical injury. Proteins whose plasma concentrations dramatically increase following infection and subsequent proinflammatory cytokine stimulation of liver hepatocytes are referred to as positive acute phase proteins, whereas those that decline are referred to as negative acute phase proteins. Many of these proteins become important mediators of immunological functions and play an active role in tissue repair and remodeling following injury. Although plasma concentrations of acute phase proteins differ markedly in their rise or decline, the APR generates a characteristic protein profile that is species-specific. Indeed, some proteins that function as an acute phase protein in one species may not be an acute phase protein in another species. Additionally, although some acute phase proteins may have a direct role in the immune responses, such as activation of macrophages and tissue repair and remodeling, others may have more of an indirect role by acting as transport proteins for products generated during the inflammatory process. For a more detailed and comprehensive review of the regulation of acute phase proteins in domestic livestock, the reader is referred to the review by Petersen et al. (2004).

PROINFLAMMATORY CYTOKINE REGULATION OF THE SOMATOTROPIC AXIS

Sheep

Within the domestic livestock arena (i.e., sheep, cattle, and pigs), elucidating the potential communication pathways between the immune system and somatotropic axis has been explored most extensively in sheep. Whereas early investigations demonstrated that intravenous administration of endotoxin (LPS) increases circulating concentrations of TNF-α (Figure 1) and GH (Figure 2) secretion in sheep (Coleman et al., 1993), the communication pathway(s) that mediate the effect on the somatotropic axis remained relatively unknown until recently. Whether LPS-induced GH secretion was mediated through the systemic release of proinflammatory cytokines from macrophages and monocytes, acting at the level of the hypothalamus, pituitary gland, or both, or whether LPS-induced GH secretion was mediated via afferent limbs of the vagus nerve, was unknown. Figure 3 depicts potential pathways by which endotoxin exposure could potentially increase pituitary release of GH in sheep.

To ascertain whether systemic proinflammatory cytokine release could be involved in the regulation of GH release, Daniel et al. (2005) conducted a series of experiments to determine if intravenous injections of TNF-α and IL-1β would increase growth hormone release in sheep. Results from their study demonstrated that intravenous injections of TNF-α and IL-1β induce a rapid increase in circulating concentrations of GH,

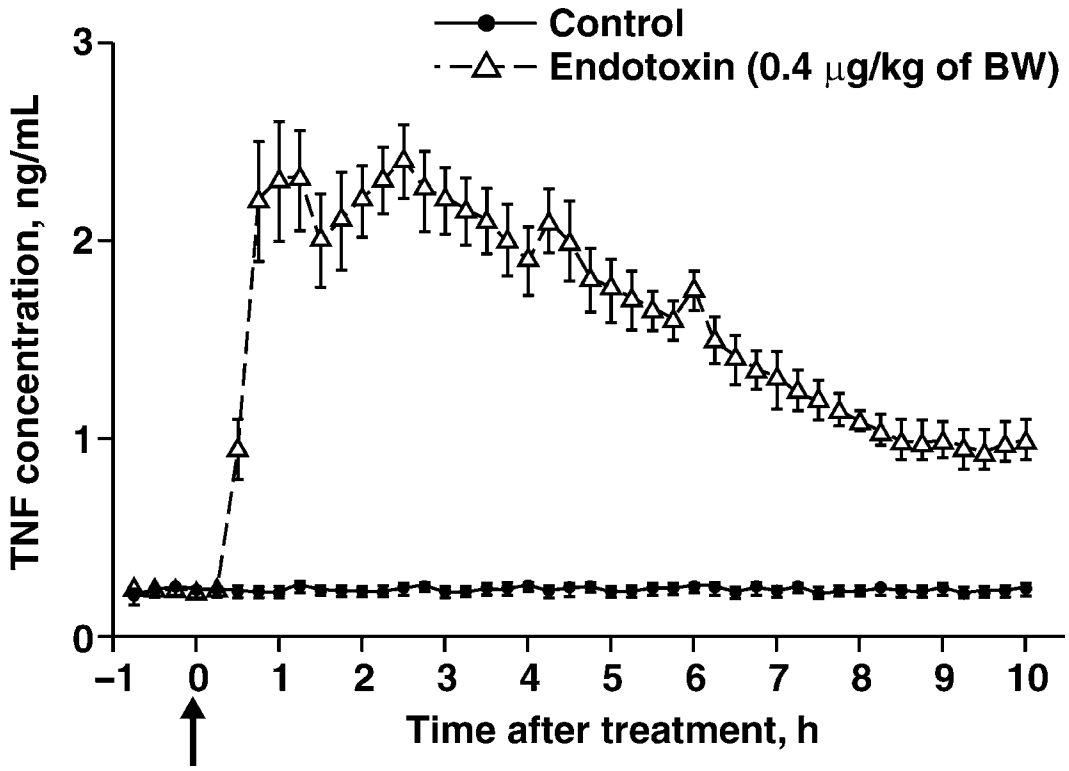

Figure 1. Effect of an endotoxin challenge (*Escherichia coli* O55:B5, Sigma, St. Louis, MO) on plasma concentrations of tumor necrosis factor-alpha (TNF) in saline- (-●- control) and endotoxin-treated (-●- endotoxin) Suffolk-cross wethers. The arrow indicates the time at which endotoxin (0.4 μg/kg of BW) was administered. Treatment × time interaction ($P < 0.0001$). (From Coleman et al., 1993).

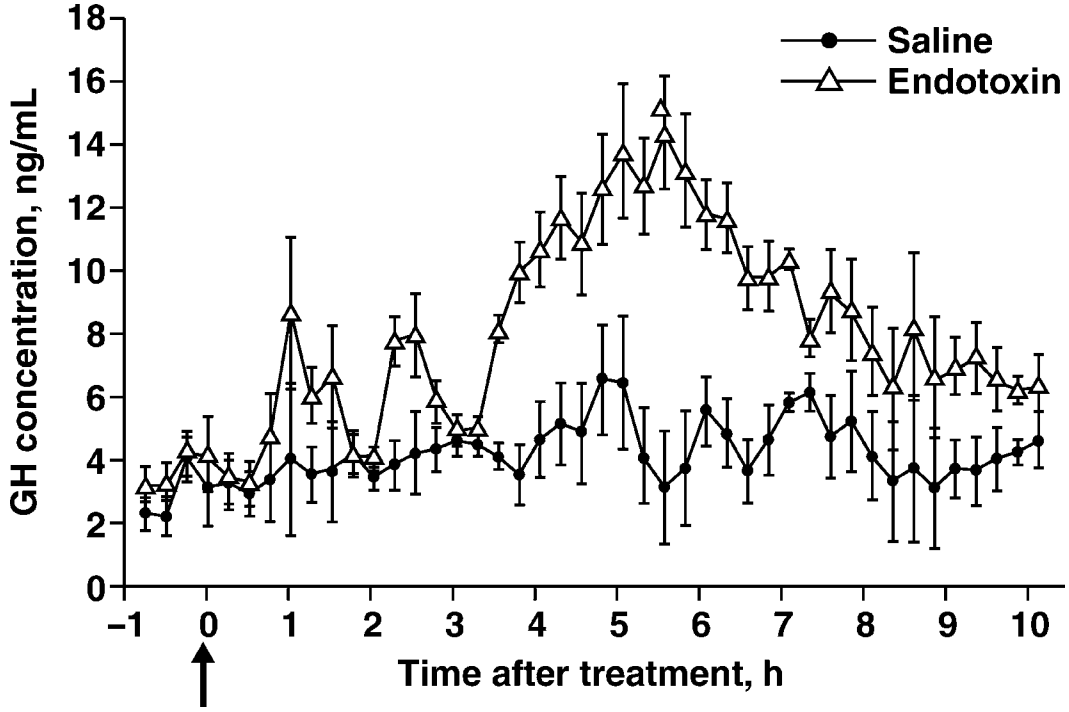

Figure 2. Effect of an endotoxin challenge (*Escherichia coli* 055:B5, Sigma, St. Louis, MO) on plasma concentrations of growth hormone in saline (-●- control) and endotoxin treated (-●- endotoxin) Suffolk-cross wethers. The arrow indicates the time at which endotoxin (0.4 μg/kg BW) was administered. Treatment effect, $P < 0.01$. (From Coleman et al., 1993).

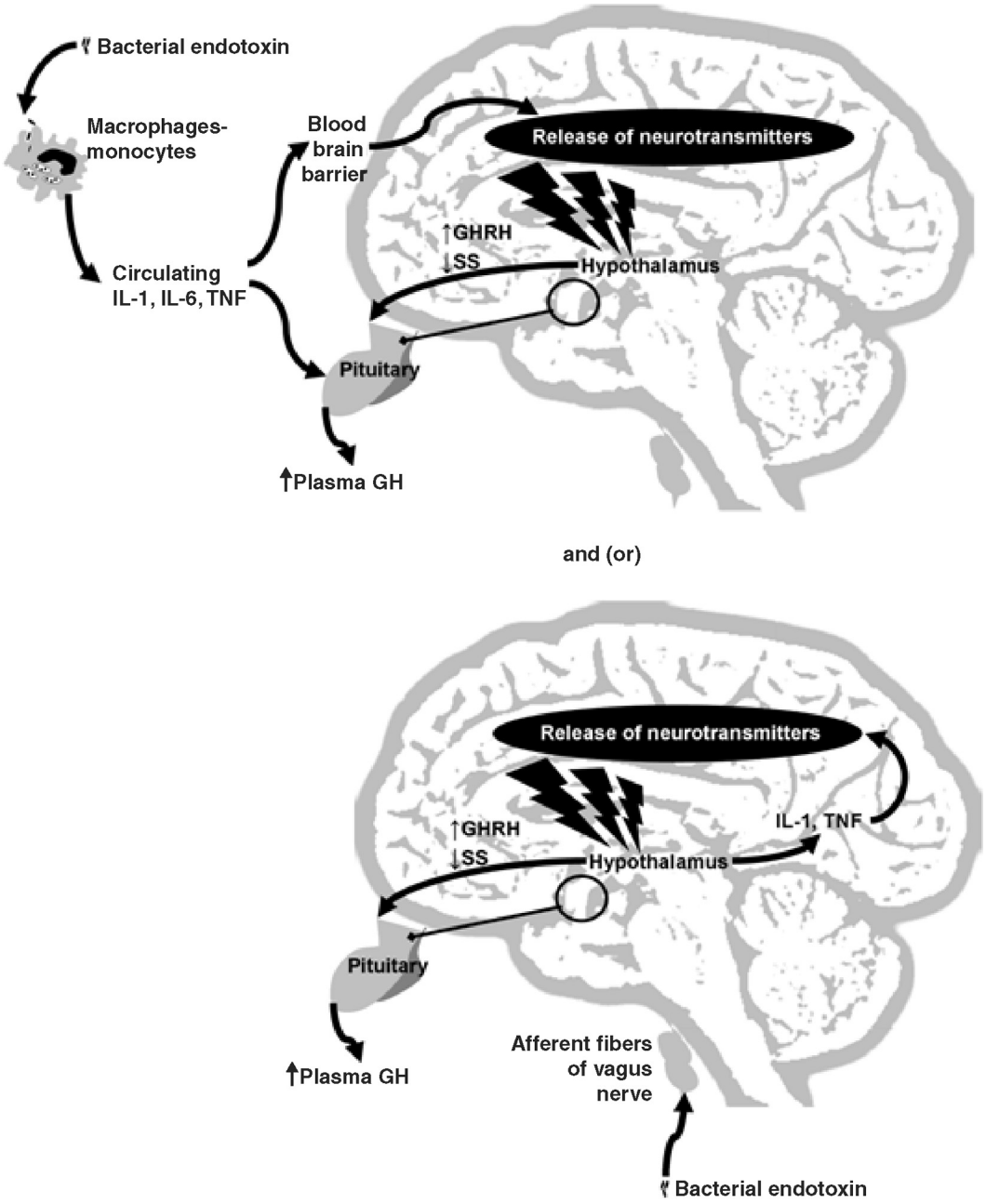

Figure 3. Potential pathways by which endotoxin exposure could increase pituitary release of growth hormone in sheep. Potential pathways include systemic release of proinflammatory cytokines from macrophages and monocytes, acting at the level of the hypothalamus, pituitary gland, or both, and mediated via afferent limbs of the vagus nerve. Abbreviations are interleukin-1 beta (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF), growth hormone (GH), growth hormone-releasing hormone (GHRH), and somatostatin (SS).

which occurred in a biphasic manner that lasted for more than 2 h (Figure 4). These authors also demonstrated that this effect could be blocked by administering a human IL-1 receptor antagonist or by administering a soluble TNF receptor-1. Collectively, results from this research indicated that endotoxin could potentially be mediating GH release via a direct action on the hypothalamus possibly through the regulation of somatostatin (**SRIH**), GHRH, or both.

Previous in vivo research by Briard et al. (1998) also supported a potential hypothalamic pathway by which LPS increased GH secretion in sheep. In that study, it was reported that a sustained increase in circulating concentrations of GH was associated with an increase in jugular and hypophyseal portal blood SRIH concentrations, although no significant changes in GHRH concentrations were observed. In an attempt to further clarify a possible intrahypothalamic pathway by which peripheral LPS increases circulating GH, Daniel et al. (2005) conducted a series of robust intracerebroventricular (**ICV**) experiments in which they injected the proinflammatory cytokines ovine IL-1β and human TNF-

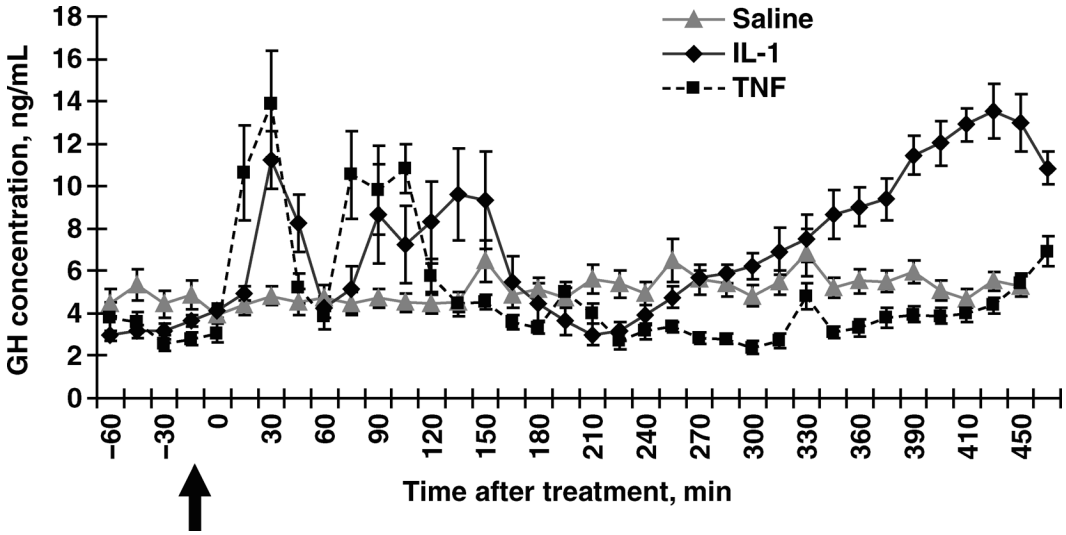

Figure 4. Effect of intravenous administration of saline (SAL), 5 μg/kg of BW of recombinant human tumor necrosis factor-α (TNF; PeproTech, Rocky Hill, NJ), and 5 μg/kg of BW recombinant ovine IL-1β (IL-1; G. Barcham, University of Melbourne, Parkville, Victoria, Australia) on plasma concentrations of GH in Hampshire-Suffolk cross wethers. The arrow indicates time at which treatments were administered. Effect of treatment, $P < 0.05$. (From Daniel et al., 2005).

α into sheep and evaluated the GH response. Those authors reported that neither IL-1β nor TNF-α significantly increased circulating concentrations of GH. Additionally, the authors reported that ICV administration of human IL-1 receptor antagonist and human soluble TNF-receptor 1 failed to blunt the increase in circulating GH following ICV injections of LPS. Therefore, whereas these results demonstrated that ICV administration of LPS could indeed increase GH secretion, it was concluded that this effect did not appear to be mediated locally through hypothalamic receptors.

Coleman et al. (1993) had already demonstrated that treating cultured ovine pituitary cells with LPS resulted in an increase in release of GH (Figure 5), thus suggesting the presence of a putative intrapituitary LPS recognition receptor and perhaps the ability of locally produced proinflammatory cytokines to stimulate the release of GH from somatotropes. Through a series of in vitro experiments, Fry et al. (1998) later demonstrated that treating cultured ovine pituitary cells with recombinant ovine IL-1β, but not recombinant bovine TNF-α, increased concentration of GH in culture medium (Figure 6). Their results demonstrated that IL-1β treatment increased both GH mRNA (~40%) and GH content (~60%), which demonstrated that IL-1β was not merely causing cell death and associated release of GH in cultured ovine pituitary cells. The authors suggested that due to the similarity between the signal transduction pathways for IL-1β and LPS, LPS may indeed elicit intrapituitary production of IL-1β, which then acts as a stimulus for GH secretion. With regard to the presence of a putative intrapituitary LPS recognition receptor, several opportunities existed because recognition of PAMP molecules, such as LPS, is mediated through a structurally diverse set of pattern-recognition receptors that belong to several different protein families (Medzhitov and Janeway, 1997). These pattern-recognition receptors can generally be divided into 3 functional groups: 1) circulating humoral proteins, such as the endotoxin receptor cluster of differentiation 14 (**CD14**) and complement proteins; 2) endocytic receptors that are expressed on the cell surface and mediate endocytosis; and 3) signaling receptors, such as toll-like receptors (**TLR**) that are expressed on the surface of the cell (Mann, 2001). In 2005, the existence of a putative intrapituitary LPS receptor in sheep became apparent when Daniel et al. reported that CD14 was colocalized

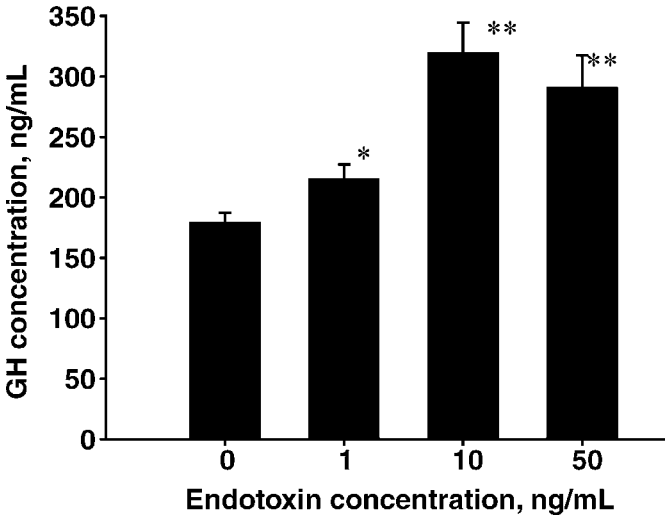

Figure 5. Effect of an endotoxin challenge (*Escherichia coli* O55:B5, Sigma, St. Louis, MO) on media concentrations of GH in cultured ovine pituitary cells. Effects of treatment, $^{*}P < 0.0$, $^{**}P < 0.01$. (From Coleman et al., 1993).

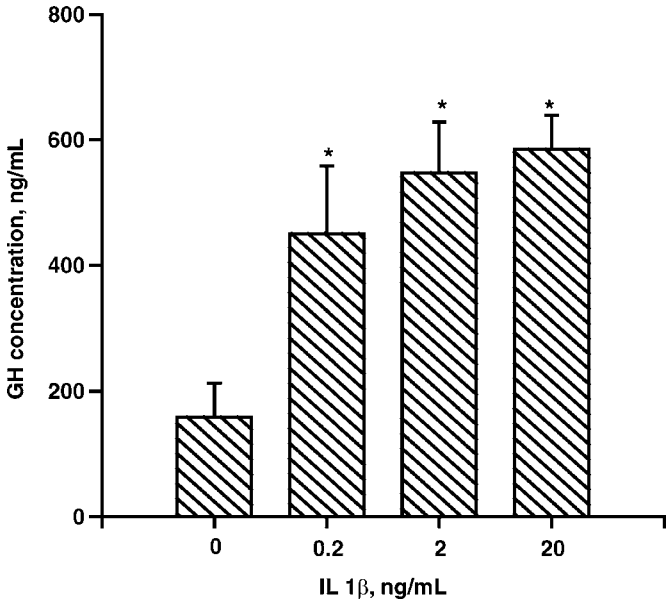

Figure 6. Effect of recombinant ovine IL-1β (provided by A. Andrews, Sydney, Australia) on media concentrations of GH from ovine pituitary cells after 20 h of culture. Effect of treatment, *$P < 0.05$. (From Fry et al., 1998).

on GH-positive cells within ovine pituitary cells (Daniel et al., 2005).

In addition to the aforementioned effects of endotoxin and proinflammatory cytokines on GH secretion, there is evidence that mediators of the acute phase immune response can also have regulatory actions on IGF-I and its associated binding proteins. In vivo work by Briard et al. (1998, 2000) demonstrated that endotoxin caused a moderate decrease in IGF-I and increased IGFBP-1 plasma concentrations in sheep in the presence of a sustained biphasic increase in GH secretion. However, no significant changes in IGFBP-2, -3, or -4 were observed. Therefore, the authors suggested that increases in circulating concentrations of IGFBP-1 may cause a state of resistance to GH because IGFBP-1 has been reported to inhibit IGF actions by binding IGF receptors, which could change IGF-I bioavailability and action. They also suggested that the endotoxin-induced alterations in the IGF-I/IGFBP system could be associated with the endotoxin-induced increase in SRIH that they previously reported in sheep (Briard et al., 1998).

Cattle

Hormonal modulation of the immune system in cattle is not a new or novel concept within the scientific arena. In fact, several researchers have engaged in this area of science for more than 2 decades (Kelley et al., 1982; Kelley, 1984; Elsasser et al., 1986). In many of the initial investigations, the focus tended to be targeted on the use of exogenous GH to enhance cell-mediated and humoral immunity in cattle (Burton et al., 1991, 1992). For example, Burton et al. (1991) demonstrated that administration of GH to dairy cows, injected at doses routinely used to increase milk yield, increased the in vitro proliferative responsiveness of lymphocytes to a mitogenic challenge. Today, however, our knowledge base has vastly increased with regard to the communication between the immune system and the somatotropic axis in cattle, and the existence of a bidirectional communication network has clearly emerged.

Some of the first associations between the proinflammatory response to infection and the lasting impacts on the somatotropic axis were described and characterized through a series of experiments with cattle performed by Elsasser et al. during the mid 1980s and early 1990s (Elsasser et al., 1986, 1988; Fayer and Elsasser, 1991). The initial work that reported the establishment and validation of a RIA for bovine TNF-α, as well as increases in peripheral concentrations of TNF-α following an endotoxin challenge in calves, was undoubtedly a critical step toward identifying the relationships between the immune system and somatotropic axis in cattle (Kenison et al., 1990). Several aspects of the communication network that are now known to exist between the immune system and the somatotropic axis were elucidated through experiments that used the traditional LPS challenge model, as well as the proinflammatory response to systemic parasite challenges in calves (Elsasser et al., 1990). Through these early investigations, it was demonstrated that the onset of an intense proinflammatory response following infection with a coccidia-like parasite (e.g., *Sarcocystis cruzi*) occurred around 27 to 28 d after infection, which produced similar physiological responses as observed in LPS-challenged calves (Elsasser et al., 1988). In those experiments, it was demonstrated that following the onset of the parasitic proinflammatory response, circulating concentrations of IGF-I were lower in infected calves as compared with noninfected control and pair-fed calves (Table 2). The reduction in plasma concentrations of IGF-I observed in the parasite-infected calves lasted throughout the entire 58-d experiment, whereas lower IGF-I concentrations were only observed on d 27 and 35 for the pair-fed calves. The results from that study clearly demonstrated that reduced IGF-I concentrations following a proinflammatory response could not be attributed solely to the anorexic behavior and associated decrease in feed intake normally observed in sick animals.

Elsasser et al. (1991) demonstrated that supplementing calves with exogenous GH reduced circulating concentrations of TNF-α following an endotoxin challenge. Subsequent research by that group demonstrated that not only was GH able to reduce endotoxin-induced TNF-α secretion, but that GH treatment reduced the hepatic TNF-α binding capacity by 40%, thus indicating that GH elicits immunomodulatory actions within multiple target tissues (Elsasser et al., 1994). Given the potential for exogenous GH to reduce the proinflammatory response in cattle, Elsasser et al. (1998) conducted further investigations to test the effi-

Table 2. Influence of a parasite infection, *Sarcocystis cruzi*, and plane of nutrition on circulating concentrations of IGF-I in calves[1]

Time relative to infection[2]	IGF-I, nmol/L		
	Control	Infected	Pair-fed[3]
Pre-	9.7	11.3	11.6
+27[4]	10.1	3.1*	5.3*
+35	10.3	1.9*	6.4*
+42	10.1	2.7*	8.7
+58	10.2	3.3*	9.1

[1]From Elsasser et al. (1988).
[2]Days postinfection with the parasite *Sarcocystis cruzi* (oral dose of 250,000 oocysts per calf).
[3]Calves that were pair-fed to match the intake of *Sarcocystis cruzi*-infected calves.
[4]Time after infection at which an intense proinflammatory response occurs.
*Denotes values that are less than ($P < 0.05$) control values.

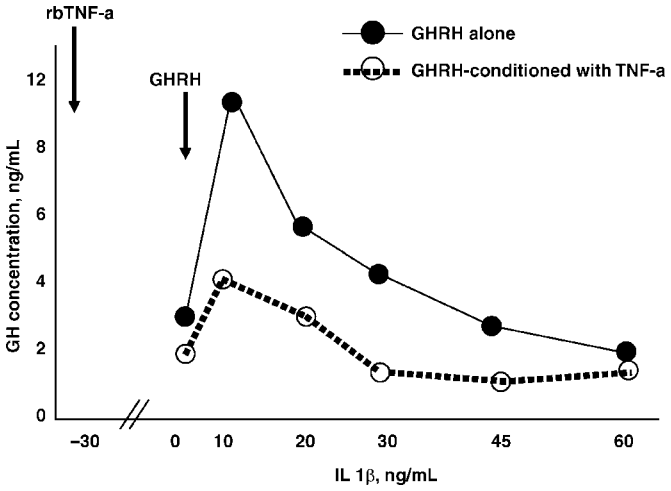

Figure 7. Effect of 30-min prior exposure to 1,250 ng/kg of BW recombinant bovine tumor necrosis factor-alpha (rbTNF-α) on secretion of GH induced by GHRH (0.1 μg/kg of BW) in calves (arrows show the time of administration of rbTNF-α and GHRH). Effect of treatment, $P < 0.05$. (From Elsasser et al., 1991).

cacy of daily injections of exogenous GH treatment as a means to reduce the detrimental effects associated with a multistage protozoan parasitic disease in cattle. It was reported that regardless of GH treatment, parasitic infection increased plasma concentrations of TNF-α at 28 d postinfection. As expected, GH treatment did increase circulating concentrations IGF-I in control calves; however, it did not prevent the parasitic-induced reduction in IGF-I. Decreases in hepatic mRNA for GH receptor and IGF-I in infected calves at the end of the experiment were also observed (Table 3). The authors suggested that the proinflammatory response on d 28 postinfection exceeded the ability of GH to maintain elevated plasma concentrations of IGF-I.

Further evidence to support the existence of a bidirectional communication network between the immune system and somatotropic axis was revealed in research investigating the effects of recombinant bovine TNF-α on basal plasma concentrations of GH, thyrotropin-releasing hormone (**TRH**)-stimulated release of GH, and GHRH-stimulated release of GH in cattle (Elsasser et al., 1991). In that particular study, it was reported that administering TNF-α did not affect basal plasma concentrations of GH. However, pretreatment of calves with TNF-α 30 min prior to TRH or GHRH treatment significantly reduced the GH response (Figure 7). Likewise, the in vitro results from that study demonstrated that treatment of pituitary tissue with TNF-α reduced the media concentration of GH following stimulation with TRH or GHRH (Figure 8). Additionally, through ligand-binding assays, those authors were able to demonstrate specific binding of recombinant bovine TNF-

Table 3. Effect of growth hormone administration on *Sarcocystis cruzi*-induced changes in immune system and somatotropic axis parameters[1]

Parameter[2]	No GH[3]		GH[4]	
	Control	Infected	Control	Infected
Plasma TNF-α,[5] pg/mL	80.0	105.2*	72.0	108.6*
Plasma IGF-I,[6] ng/mL	142	94*	161	98*
Plasma urea,[7] mg %	10.7	13.6	9.3*	12.9
Pituitary GH content, ng/mg of protein	12.5	12.5	8.6*	8.8*
GH receptor[8]	5.2	2.6*	3.4	2.5*

[1]From Elsasser et al. (1988).
[2]Parameters measured at 28 d postinfection with the parasite *Sarcocystis cruzi* (oral dose of 250,000 oocysts per calf).
[3]Noninfected (control) and infected calves that did not receive GH treatment.
[4]Noninfected (control) and infected calves that received daily i.m. injections of GH [USDA-bGH-B1, 12.5 mg/(calf·day)] from d 20 to 56 postinfection.
[5]Plasma concentration of tumor necrosis factor-alpha.
[6]Plasma concentration of insulin-like growth factor I.
[7]Percentage change in plasma concentration of urea.
[8]Hepatic GH receptor number.
*Denotes values that are lower ($P < 0.05$) than control values.

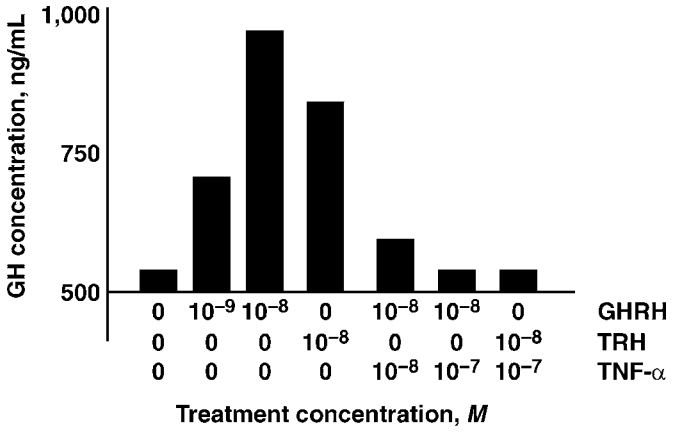

Figure 8. In vitro effects of recombinant bovine tumor necrosis factor-alpha (TNF-α) on media concentrations of thyrotropin-releasing hormone (TRH) and GHRH stimulated release of GH from bovine pituitary slices. Both TRH and GHRH stimulated release of GH was reduced ($P < 0.05$) by treatment with TNF-α. (From Elsasser et al., 1991).

α, thus indicating existence of TNF-α receptors within the bovine pituitary gland.

In a recent study, Li et al. (2007) provided even more evidence supporting an intricate communication network between the immune system and somatotropic axis in cattle at the intracellular level. In that study, the ability of GH treatment to modulate changes in inducible nitric oxide and signal transduction pathway elements in the liver following an LPS challenge was investigated. Results revealed that daily injections of exogenous GH not only augmented LPS-induced production of inducible nitric oxide within the liver, but also differentially altered the signal transduction pathway elements within the liver following LPS activation.

Swine

Although relationships between the immune system and somatotropic axis in swine have been recognized for more than 15 yr, elucidation of the intricate communication network that has been reported in other domestic livestock has not been as extensively identified in swine. However, sufficient evidence within the literature does indeed support the existence of a bidirectional communication network between the immune system and somatotropic axis in swine. As in sheep and cattle, initial investigations focused primarily on the responsiveness of the immune system following exogenous GH treatment (Weigent et al., 1990; Gala, 1991; Kelley et al., 1992). However, some of these early investigations reported no significant effect of GH treatment on the overall health or specific immunological variables in swine. For example, Goff et al. (1991) reported that administration of GH over a period of 57 d did not significantly affect total and differential white blood cell counts, lymphocyte proliferation in response to mitogens, chemotactic neutrophil function, or antibody-dependent cell-mediated cytotoxicity. Subsequent research, however, indicated that the initial contradictory reports associated with GH treatment were most likely due to animal numbers, dosages and duration of GH treatment, method of GH administration, or a combination of these (Wise et al., 1994).

In the late 1990s, several studies were published that provided additional insight into the relationship between the immune system and the somatotropic axis in swine. In 1997, Myers et al. (1997) reported that treatment of growing pigs with GH from 60 to 90 kg of BW reduced LPS-induced TNF-α secretion and the adverse metabolic effects of LPS-induced septic shock. However, no effect of GH treatment on the proinflammatory cytokine IL-6 was observed. During that same year, Hevener et al. (1997) demonstrated an acute increase in circulating concentrations of GH at 40 min following an intraperitoneal challenge with LPS in finishing pigs. However, it was reported that this effect was only short-lived, and the subsequent LPS-induced uncoupling of the GH/IGF-I axis persisted for 96 h post-challenge. Previous research had also demonstrated acute increases in circulating concentrations of GH in pigs during the first 20 min following an LPS challenge (Parrott et al., 1995). Hevener et al. (1997) attributed the persistent uncoupling of the GH/IGF-I axis to factors beyond nutritional influences because feed consumption did not differ between control and LPS-challenged pigs, a hypothesis similar to that previously proposed in cattle (Elsasser et al., 1988). In a later study by Wright et al. (2000), it was reported that a rapid LPS-induced reduction in circulating concentrations of IGF-I in weanling pigs was associated with an overall increase in circulating concentrations of GH. Those authors also reported a concurrent decrease in food consumption, suggesting a possible nutritional influence associated with the reduction in circulating concentrations of IGF-I. However, given the virtually instantaneous decrease in circulating concentrations of IGF-I and continuously low concentrations of IGF-I even after the pigs resumed normal feed consumption, it was suggested that other nonnutritional mechanisms, such as an increase in IGF-I clearance, might have contributed to this effect.

In addition to the aforementioned effects of endotoxin on somatotropic function in swine, numerous studies have documented the effects of various parasitic, viral, and bacterial diseases on somatotropic function within pigs. Prickett et al. (1992) reported that infection of young, growing pigs (14 kg of BW) with *Sarcocystis miescheriana*, a protozoan parasite, resulted in reduced weight gain following the acute phase response that occurred 15 d after infection. Additionally, lower serum concentrations of IGF-I, and elevated serum concentrations of IGFBP-1, IGFBP-2, and IGFBP-4 during the acute phase response time period were observed. Roberts and Almond (2003) demonstrated that concomitant infections with porcine reproductive and respiratory

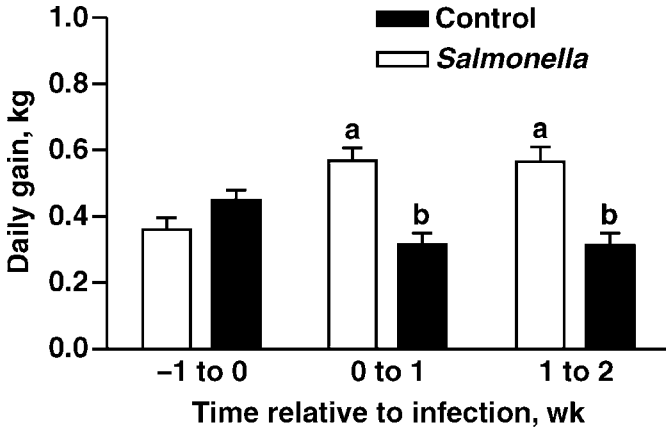

Figure 9. Daily gains in growing pigs following treatment with *Salmonella typhimurium* (3×10^9 cfu) or sterile broth (control). Effect of treatment (a vs. b), $P < 0.001$. (From Balaji et al., 2000).

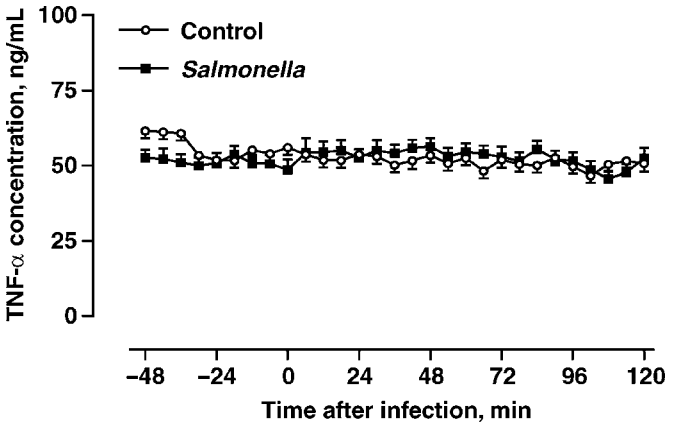

Figure 11. Plasma concentrations of tumor necrosis factor-alpha (TNF-α) in growing pigs following treatment with either *Salmonella typhimurium* (3×10^9 cfu) or sterile broth (control). Plasma concentrations of TNF-α were not different between the 2 treatment groups, $P > 0.10$. (From Balaji et al., 2000).

syndrome virus and *Mycoplasma hyopneumoniae* in growing pigs resulted in decreased concentrations of IGF-I, despite the fact that overall ADG and feed conversion did not differ between infected and noninfected pigs. As in previous studies, circulating concentrations of IGF-I were reported to have remained low even after feed intake had returned to noninfected levels. In *Salmonella typhimurium* challenge pigs, Balaji et al. (2000) reported significant reductions in daily gain (Figure 9) during the first 2 wk postinfection, and lower plasma concentrations of IGF-I from 30 to 108 h postinfection. However, no consistent alterations in circulating concentrations of GH, as a result of *Salmonella typhimurium* infection, were observed. Burkey et al. (2004) also demonstrated significant reductions in circulating concentrations of IGF-I from d 2 to 4 postinfection in weanling pigs challenged with *Salmonella typhimurium* (Figure 10). Interestingly, in the study by Balaji et al. (2000), the authors reported no effect of *Salmonella typhimurium* on plasma concentrations of TNF-α (Figure 11), despite considerable increases in rectal temperature and plasma concentrations of cortisol in infected pigs. Based on their observations in swine, as well as that of other researchers that reported no systemic increase in TNF-α following *Salmonella typhimurium* (Peel et al., 1990) or *Pasteurella hemolytica* (Espinasse et al., 1993) infection in cattle, it was suggested that systemic release of TNF-α may only be observed in situations in which septicemia occurs. A recent study by Fraser et al. (2007) provides further support for this hypothesis because results from their study demonstrated that neither *Salmonella typhimurium* nor *Salmonella choleraesuis* elicited a proinflammatory cytokine response (i.e., TNF-α and IL-1β) in pigs.

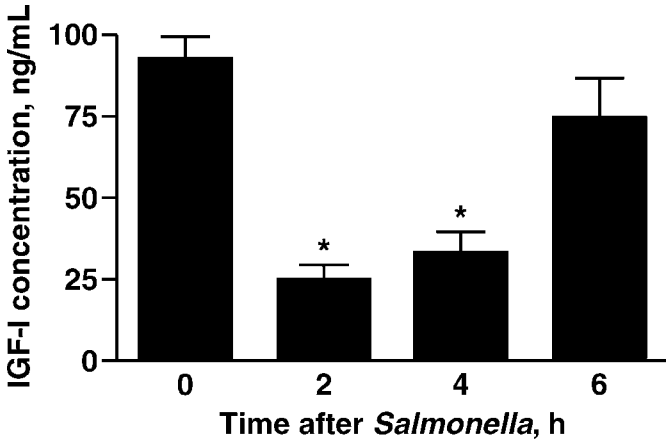

Figure 10. Effect of *Salmonella typhimurium* (1.33×10^9 cfu) on serum concentrations of insulin-like growth factor I (IGF-I) in weanling pigs. Effect of treatment, *$P < 0.001$ vs. d 0. (From Burkey et al., 2004).

CONCLUSIONS

Further clarification of the cross-communication that takes place among the endocrine, neuroendocrine, immune, and nutritional processes within the body will undoubtedly continue to be unveiled as new research tools become available and as researchers develop new in vitro and in vivo model systems to pursue the complexities associated with the regulation of the immune system. Collectively, the information provided within the current paper demonstrates that a bidirectional communication network does indeed exist in a variety of domestic livestock. Additionally, sufficient evidence exists that demonstrates that the uncoupling of the GH/IGF axis associated with an immunological challenge is influenced by nutritional and nonnutritional factors. Future research endeavors focused on intervention

strategies to reduce production-associated losses following sickness and disease could prove to be economically valuable within the livestock industry.

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